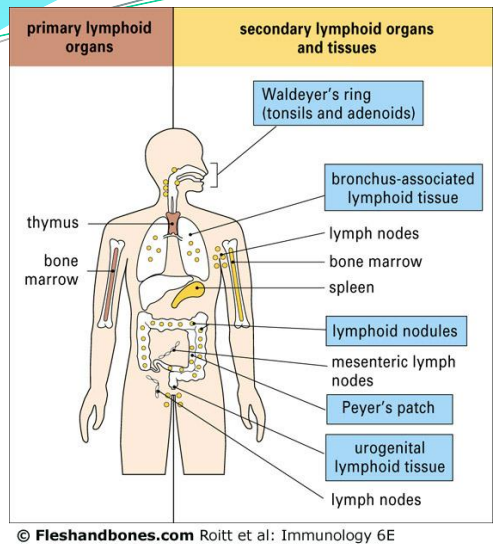

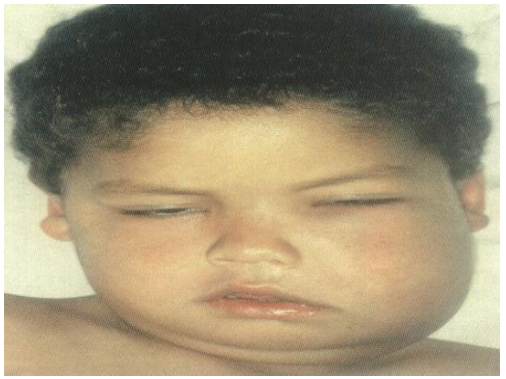

Overview of Lymphomas

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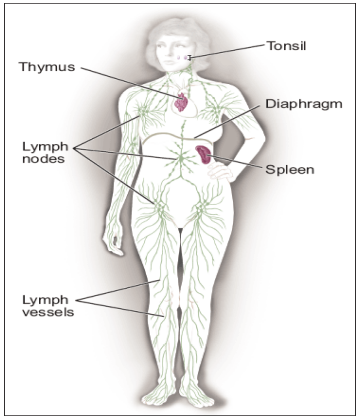


Objective

By the end of this lecture the student must be able to:

- Discriminate clinically different types of lymphoma
- Diagnose a case of Hodgkin lymphoma (HL) & it's stage
- Diagnose a case of Non Hodgkin lymphoma (NHL)& it's stage
- Identify prognostic criteria for both HL & NHL

- Refer to Essential Hematology book, 6th edition , page (246- 271)

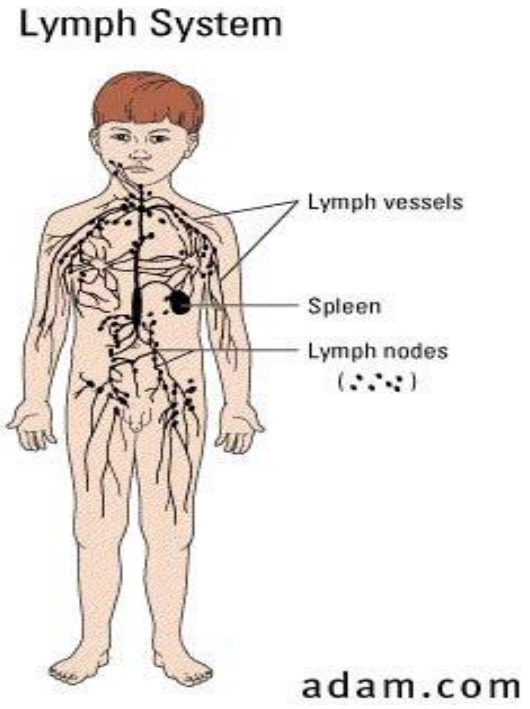
Lymphoma

- Definition: Tumour of lymphoid tissue
- Etiology: Idiopathic, Genetic, Infective.
- Clinical: Lymphadenopathy, weight loss, Fever.
- Two Major Types: & many subtypes.
- Hodgkins lymphoma (HL) – RS cells.
- Non-Hodgkins lymphoma (NHL) – no RS cells.
  - B cell, T cell & Histiocytic lymphoma.

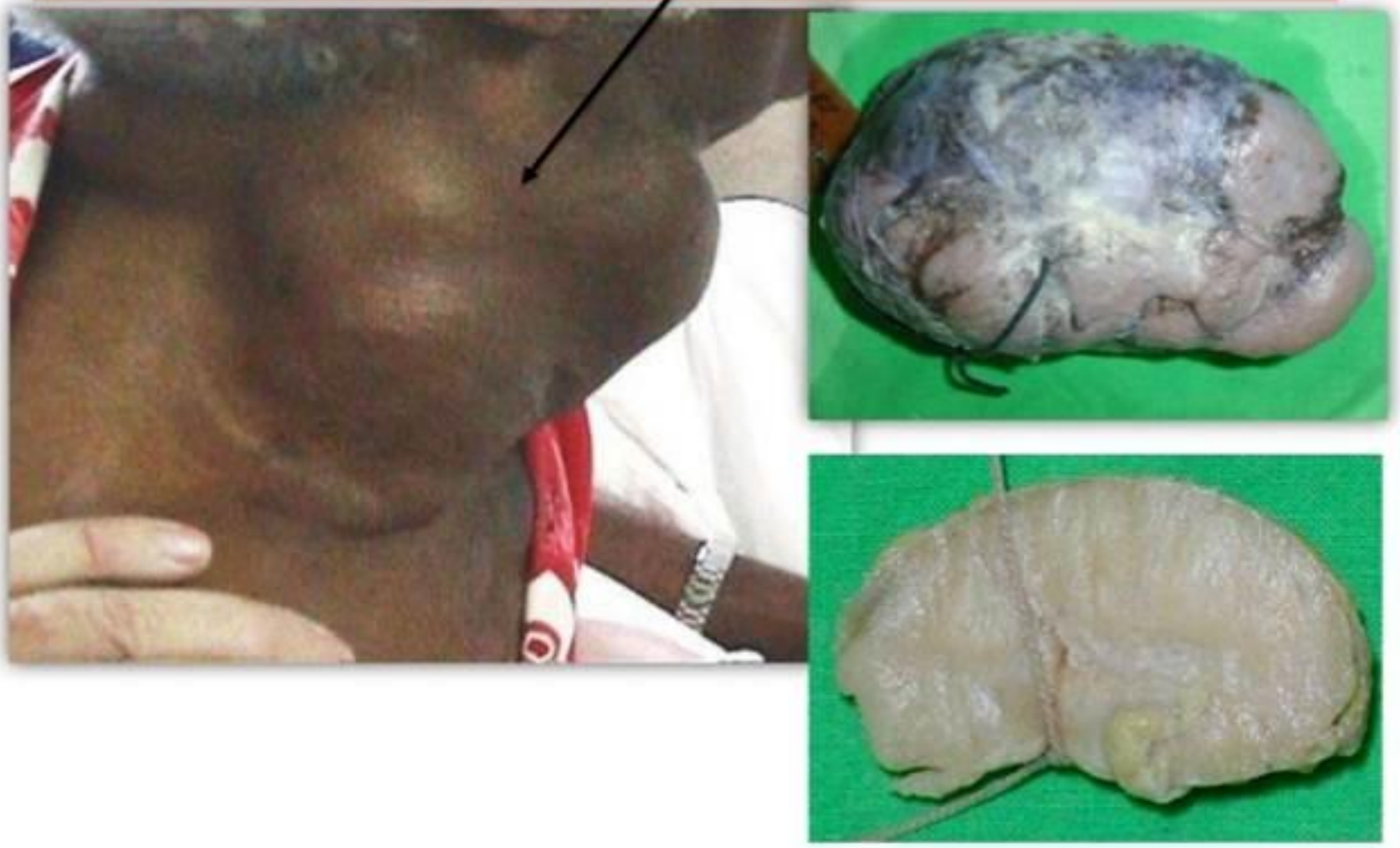
- Characterized by the **abnormal proliferation B or T cells in lymphoid tissue** cause the characteristic **lymphadenopathy**
- The lymphomas are classified by the appearance of malignant lymphocytes on biopsy of tumor
- Three categories:
  - Low-grade
  - Intermediate-grade
  - High-grade
- Prognosis is dependent on the grade and stage

Functional Presentation of Lymphoma

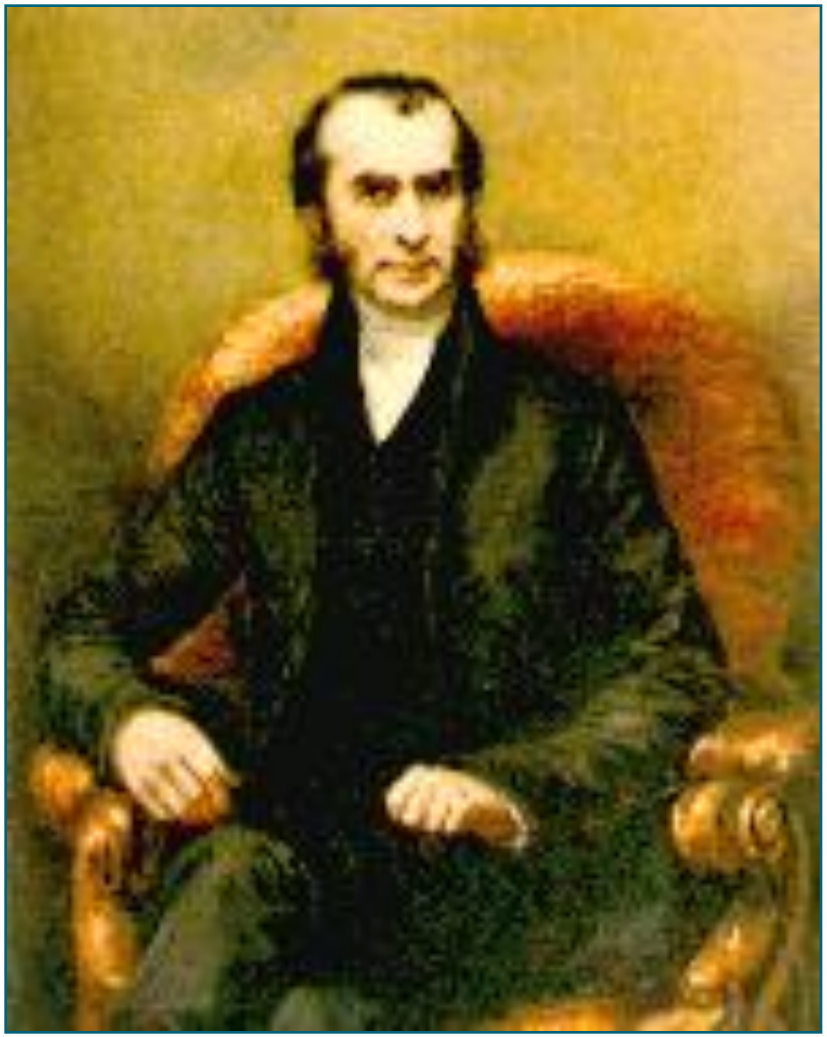
- People present with swollen, growing lymph glands (nodal disease) or tumors in other organs (extramodal disease)
- Person can be asymptomatic
- Common B symptoms include fever, drenching night sweats, loss of 10% of body weight, and pruritis (severe itching)



Lymphoma

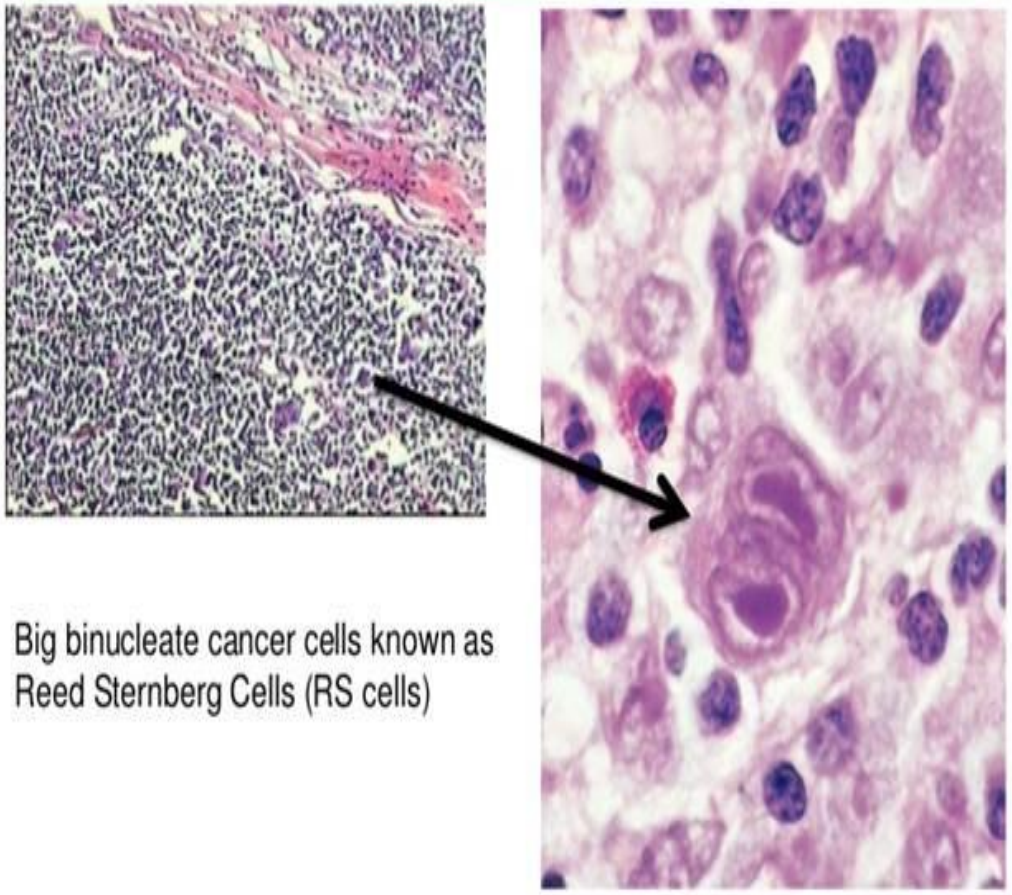


Hodgkin Lymphoma/ Disease



Thomas Hodgkin
(1798-1866)

Hodgkins Lymphoma



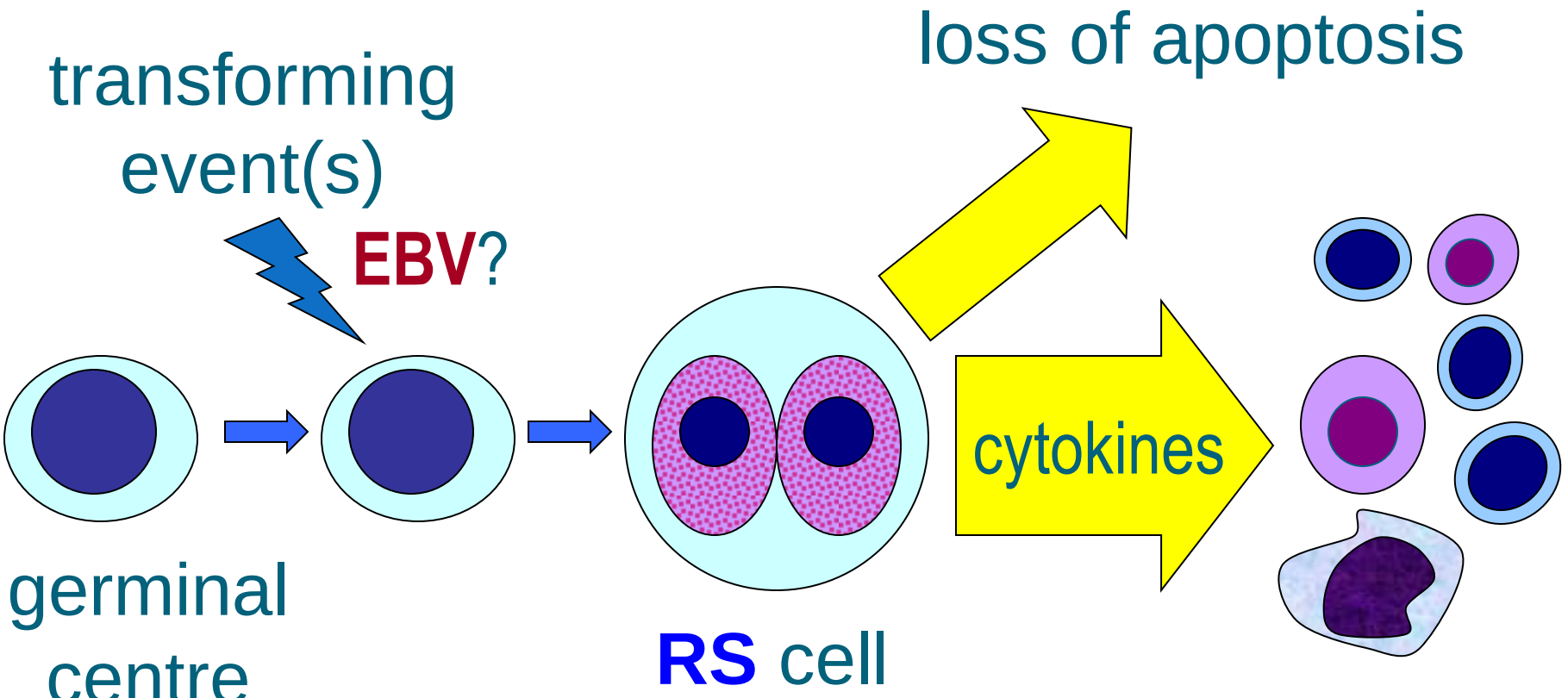
Big binucleate cancer cells known as Reed Sternberg Cells (RS cells)

- Hodgkin lymphoma (formerly called Hodgkin's disease) is a group of cancers characterized by Reed-Sternberg cells in an appropriate reactive cellular background.

- Evidence is now that the majority of classical HL have clonal Ig rearrangement, with somatic hypermutation clearly identifying that H-RS cells as a neoplastic, germinal center derived B- cells.

Etiology of HL;

A possible model of pathogenesis



Pathogenesis is unknown, but Epstein Barr virus (EBV) may be considered.

WHO; Histopathologic Classification -1997

- **Classical HL**

(RS easily detected)

(CD30+/CD15+/CD45-/panB and panT antigen)

- Nodular sclerosis – low grade
- Lymphocyte rich CHL
- Lymphocyte depletion high grade
- Mixed cellularity More aggressive
- Unclassified

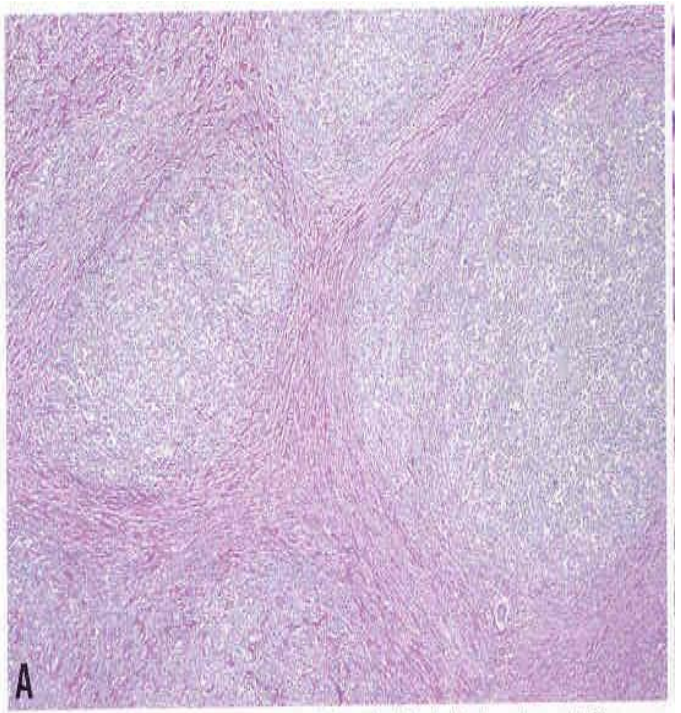


Fig. 8.21 Nodular sclerosis subtype of classical Hodgkin lymphoma. A Fibrous co

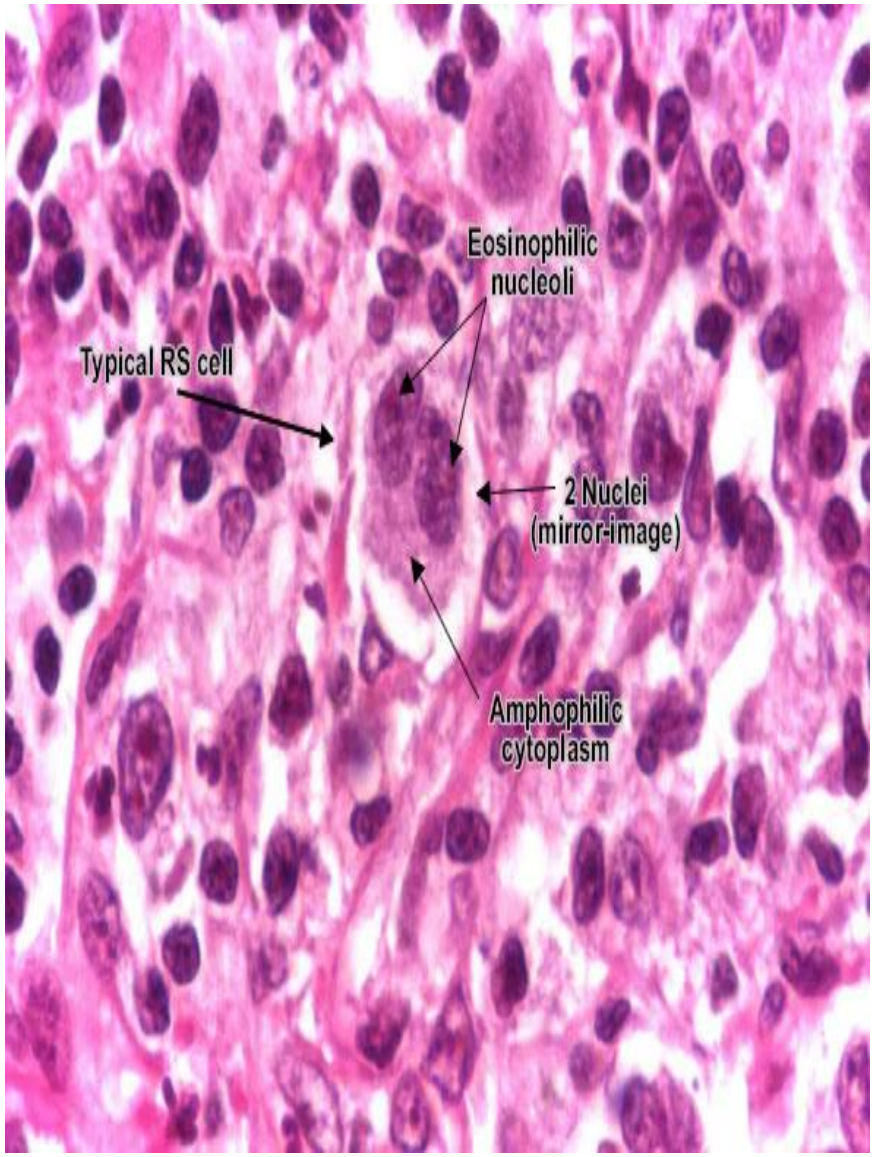
- **Nodular lymphocyte predominant**

(CD30-/CD15-/pan-Bcell +)

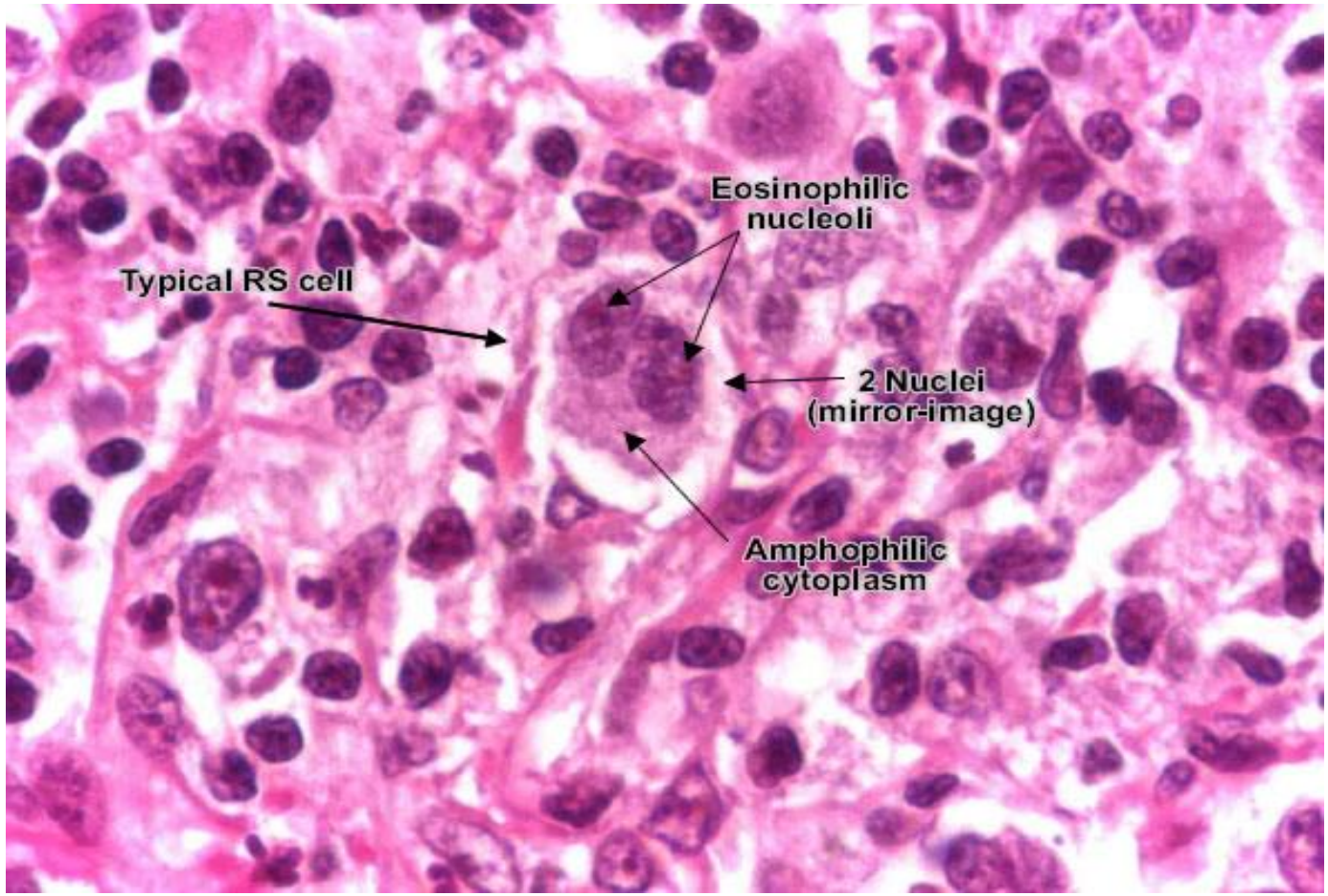
(Non classical)

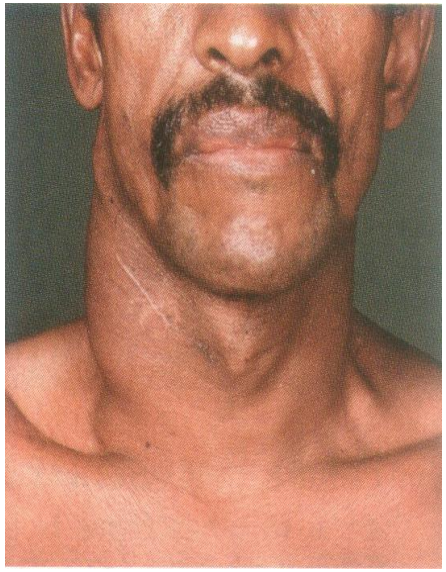
- Pathological diagnosis by lymph node biopsy, HD is characterized by Reed-Sternberg(RS) cells, they are giant cells with paired mirror image nuclei and prominent nucleoli that create the owl-eye appearance.

- Host inflammatory cells comprise the background, appear in response to cytokines liberated by RS cells, they include eosinophils, lymphocytes, neutrophils, macrophages and plasma cells. RS cells produce at least 12 cytokines (IL-1, IL-6, TNF… that could account for constitutional (B) symptoms.



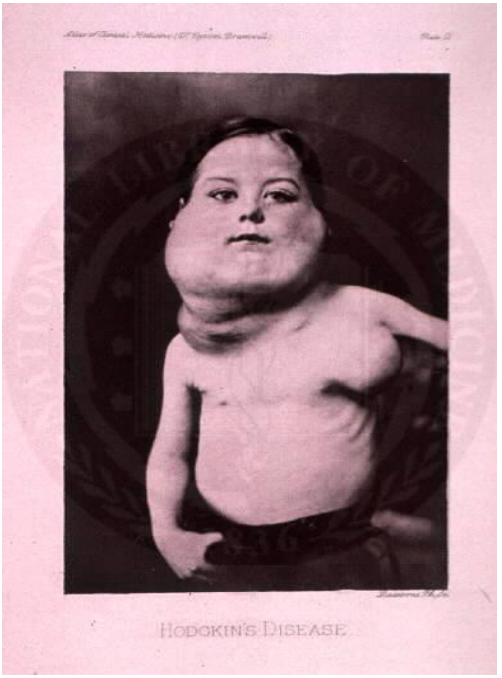
How to diagnose Hodgkin's Lymphoma





Clinical Presentation

- Bimodal distribution: peak in 20's and a second peak over age 50.
- Most will present with asymptomatic lymphadenopathy often in the neck *(Painless, non-tender, asymmetrical, firm, discrete & rubbery enlarged superficial lymph nodes).*
- Can manifest as mediastinal mass on CXR.
  - If large enough can cause symptoms such as cough, retrosternal cp
- Splenomegaly
- Hepatomegaly



Classical Hodgkin Lymphoma

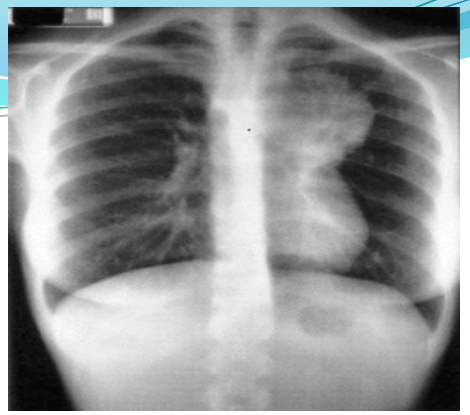
Systemic Symptoms

- Constitutional - B symptoms similar to those seen with NHL often are present:
  - Fever: *(Pel-Ebstein intermittent fever is rare)*
  - Cachexia *(progressive weakness)*
  - Night sweats
  - Weight loss
  - Fatigue
  - Generalized Pruritus: uncommon **10%-50%.**

Other possible Symptoms

- Alcohol- induced pain *(unknown)*
- Skin lesions ; urticaria, erythema multiforme, erythema nodosum, necrotizing lesions, hyperpigmentation, and skin infiltration
- Advanced disease is associated with lymphocytopenia and loss of cellular-immunity with the defiency of T-cells.
- Nephrotic syndrome
- Hypercalcemia
- Eosinophilia
- Anemia

Diagnosis



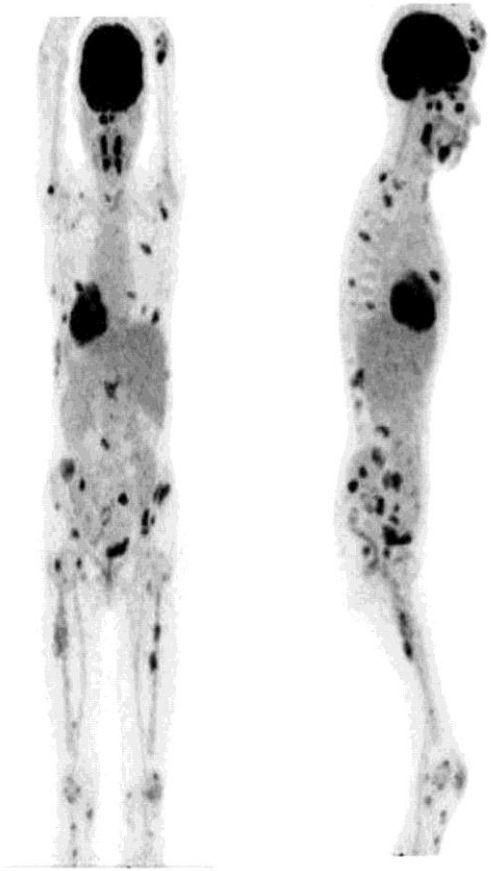
- **Lymph node biopsy:**
  The diagnosis is made by histololgical examination of an excised lymph node.

- **BLOOD**:

(FBC, Film, ESR, LFT, LDH, Urate , Ca.)

- **X-ray, CT, PET scan**.

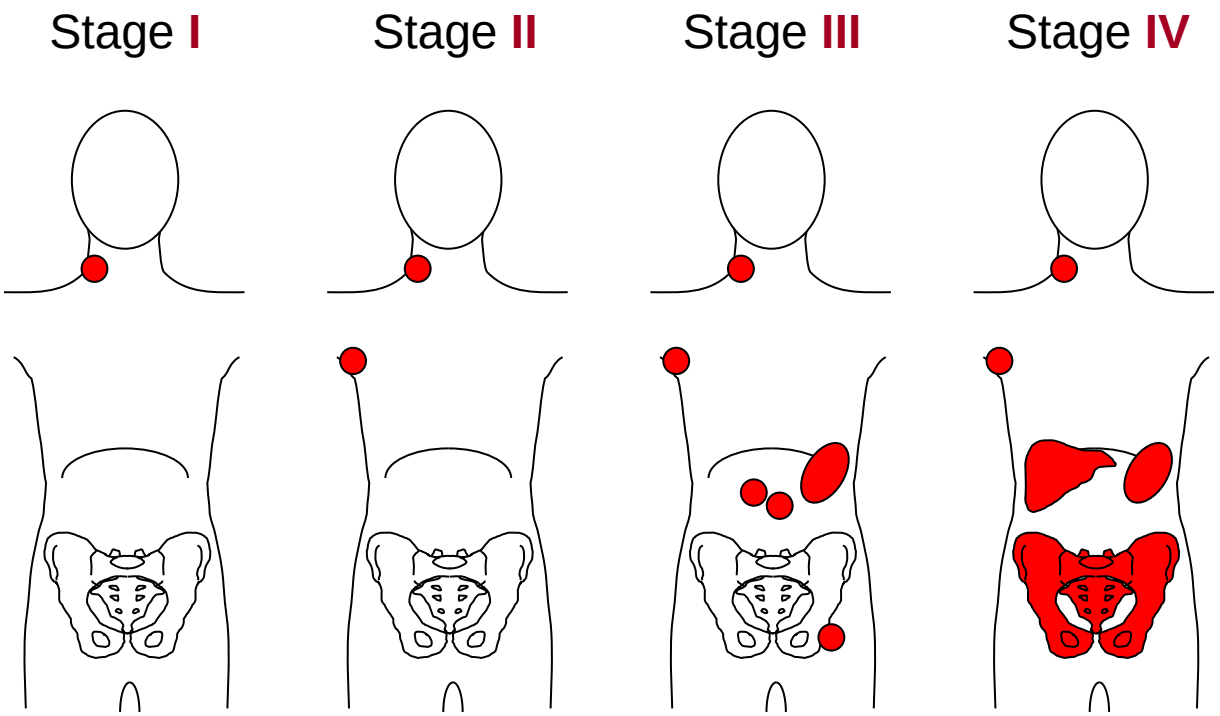
- **Bone marrow biopsy** —— staging of HI



Stages of NHL
Ann Arbor Staging System

- Stage is the term used to describe the extent of tumor that has spread through the body (**I** and **II** are localized where as **III** and **IV** are advanced.
- Each stage is then divided into categories **A**, **B**, **E** and **X**
  - **A**: No systemic symptoms
  - **B**: Systemic Symptoms such as fever, night sweats and weight loss
  - **E**: Spreading of disease from lymph node to another organ (Extranodal)
  - **X**: Bulky disease

Staging of lymphoma; HD/NHD



A: absence of B symptoms
B: fever, night sweats, weight loss

Hodgkin's Lymphoma;
Unfavorable prognostic factors:

- Stage IIIB, IV
- B symptoms
- Bulky disease
- High ESR >50

Overview of Treatment

- HD is highly curable even after relapse
- Stage and prognostic factors will determine high vs. low risk disease and will drive treatment choices

Non-Hodgkin's Lymphoma

- Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of malignant lymphomas. There are many different subtypes, every few years the classification is updated. Today, morphology, immunophenotype, molecular, cytogenetics, and other techniques are used for diagnosis.

- Treatment generally depends on the aggressiveness of the disease (indolent, aggressive, or very aggressive)

WHO/REAL Classification of Lymphoid Neoplasms

B-Cell Neoplasms

- Precursor B-cell neoplasm
  - Precursor B-lymphoblastic leukemia/lymphoma (precursor B-acute lymphoblastic leukemia)
- Mature (peripheral) B-neoplasms
- B-cell chronic lymphocytic leukemia / small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma‡
- Splenic marginal zone B-cell lymphoma (± villous lymphocytes)*
- Hairy cell leukemia
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of MALT type
- Nodal marginal zone B-cell lymphoma (± monocytoid B cells)*
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
  - Mediastinal large B-cell lymphoma
  - Primary effusion lymphoma†
- Burkitt's lymphoma/Burkitt cell leukemia§

T and NK-Cell Neoplasms

- Precursor T-cell neoplasm
  - Precursor T-lymphoblastic leukemia/lymphoma (precursor T-acute lymphoblastic leukemia

Mature (peripheral) T neoplasms

- T-cell chronic lymphocytic leukemia / small lymphocytic lymphoma
- T-cell prolymphocytic leukemia
- T-cell granular lymphocytic leukemia[II]
- Aggressive NK leukemia
- Adult T-cell lymphoma/leukemia (HTLV-1+)
- Extranodal NK/T-cell lymphoma, nasal type#
- Enteropathy-like T-cell lymphoma**
- Hepatosplenic γδ T-cell lymphoma*
- Subcutaneous panniculitis-like T-cell lymphoma*
- Mycosis fungoides/Sézary syndrome
- Anaplastic large cell lymphoma, T/null cell, primary cutaneous type
- Peripheral T-cell lymphoma, not otherwise characterized
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, T/null cell, primary systemic type

Hodgkin's Lymphoma (Hodgkin's Disease)

- Nodular lymphocyte predominance Hodgkin's lymphoma
- Classic Hodgkin's lymphoma
  - Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)
  - Lymphocyte-rich classic Hodgkin's lymphoma
  - Mixed cellularity Hodgkin's lymphoma
  - Lymphocyte depletion Hodgkin's lymphoma

‡ Formerly known as lymphoplasmacytoid lymphoma or immunocytoma

II Entities formally grouped under the heading large granular lymphocyte leukemia of T- and NK-cell types

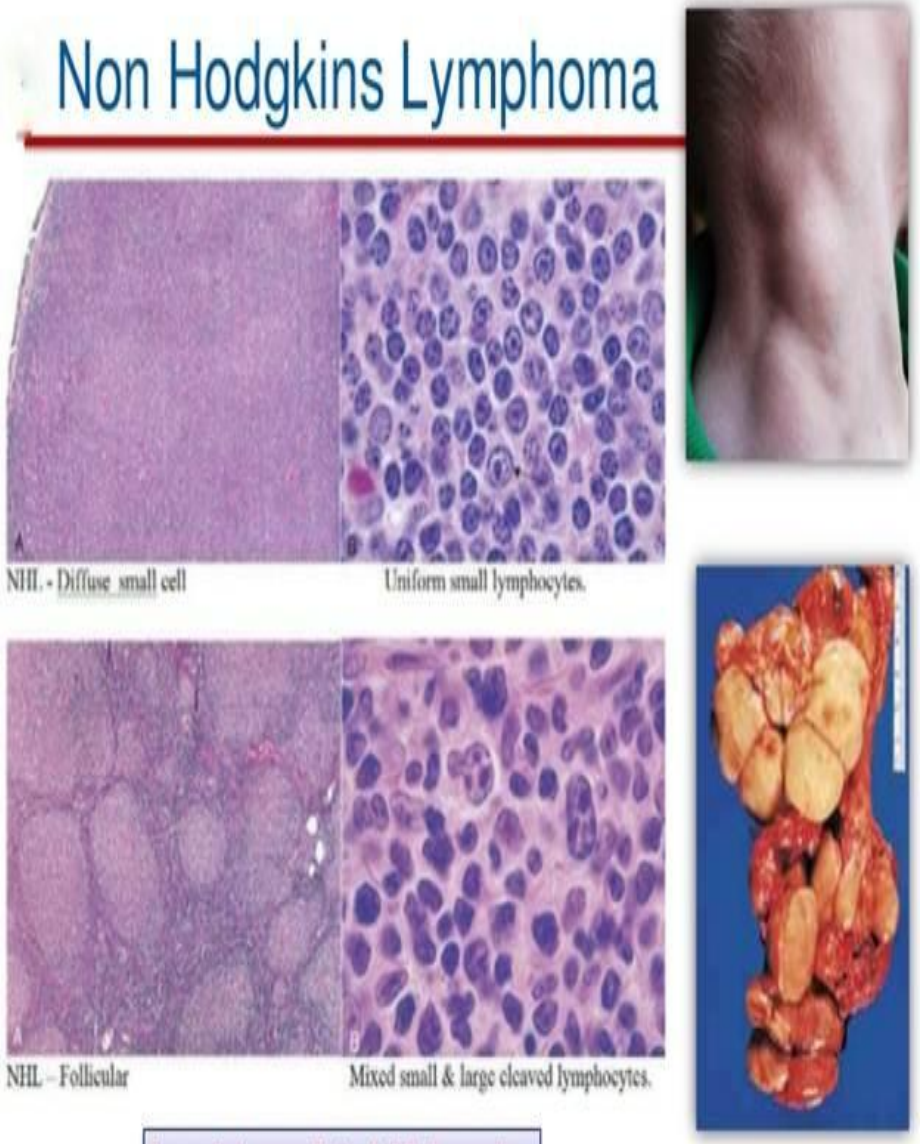
* Provisional entities in the REAL classification

† Not described in REAL classification

§ Includes the so-called Burkitt-like lymphomas

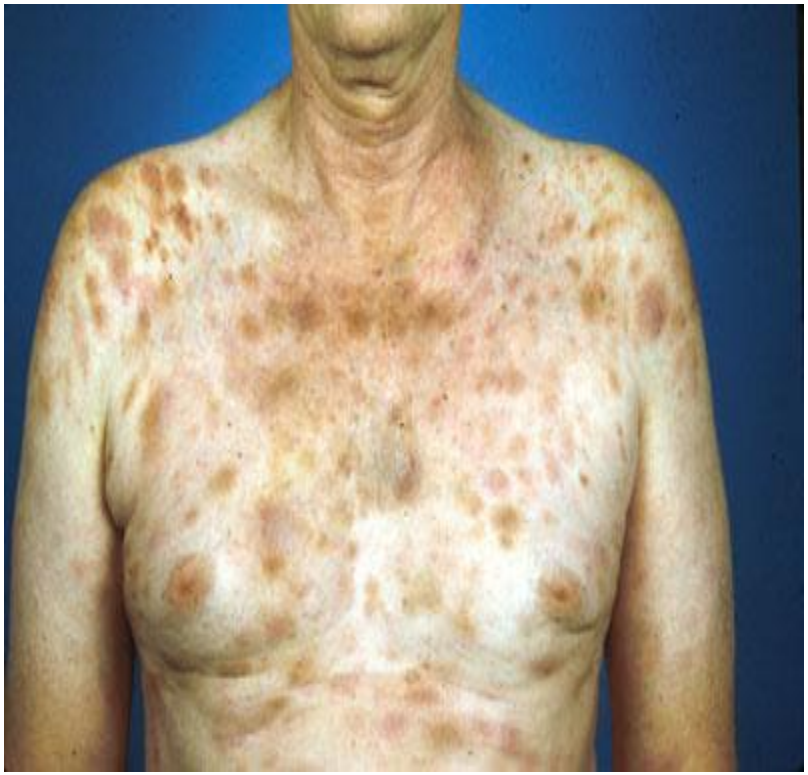
** Formerly known as intestinal T-cell lymphoma

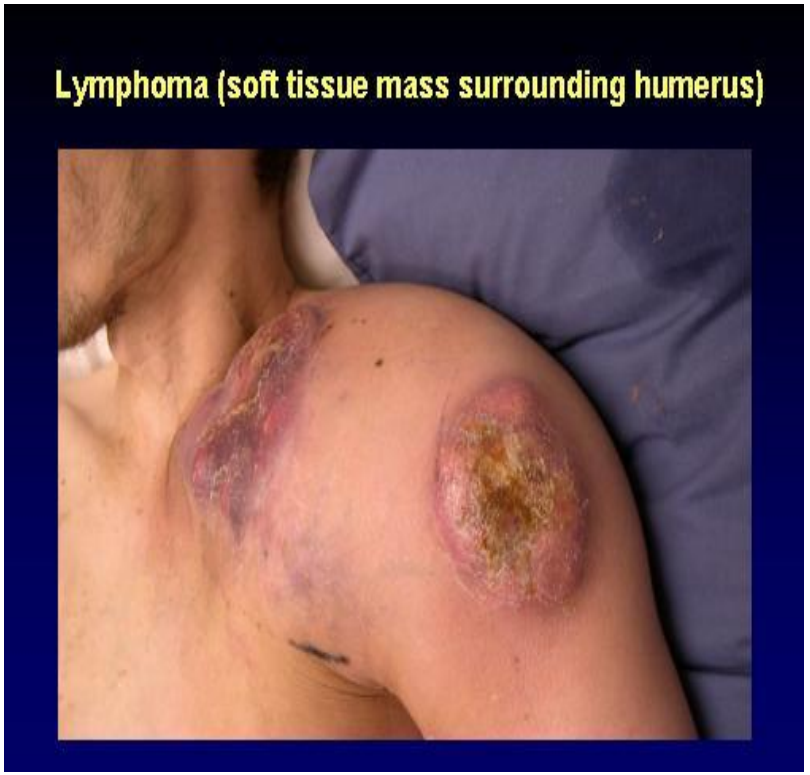
Formerly know as angiocentric lymphoma



- No RS cells or eosinophilia.
- **Complex names and classification.**
- Cell type – B, T & Histocytic "**B commonest**"
- **Histology – Follicular & diffuse.**
- **Clinical – low, intermediate & high grade.**
- **Special types** : Burkitts lymphoma, Myloma, Waldenstroms macroglobulinaemia.

Skin Lymphoma and Shoulder Lymphoma





Etiology of NHL;

- **Occupational** : Higher risk associated with several occupations: Farmers, agricultural workers chemists
- **Infection**

❖ **Viruses:**

- HTLV 1 : associated with Adult T cell Leukemia/Lymphoma
- EBV : Burkitts Lymphoma, esp in endemic form (95%),
- AIDS associated primary CNS lymphoma
- HHV8 : Kaposi's Sarcoma and primary effusion lymphoma

❖ **Helicobacter Pylori:** MALT lymphoma

- **Chromosomal translocations**

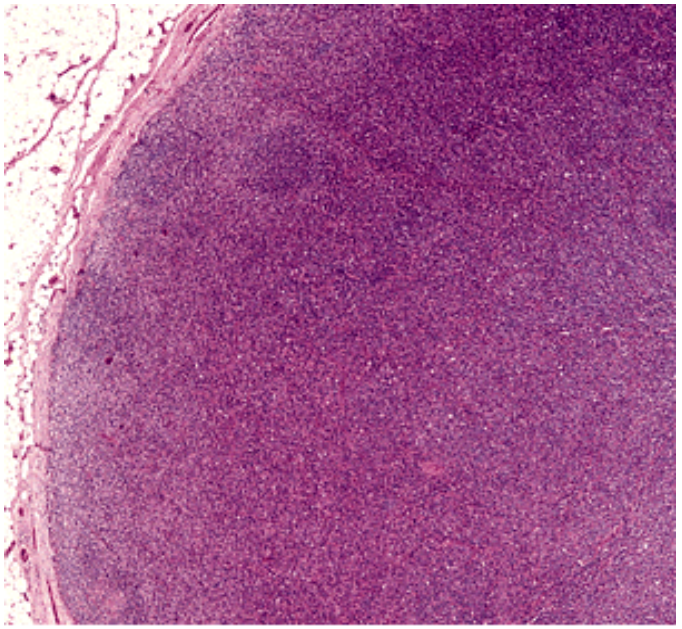
t(8:14) in Burkitts Lymphoma

t(14:18) >80% of follicular

NHL: Two Commonest subtypes

- Aggressive - Diffuse Large Cell Lymphoma
- Indolent - Follicular Lymphoma

Low grade lymphomas carry the best prognosis(the most indolent and well tolerated malignancies) and high grade ones the worst(the highly proliferative and rapidly fatal).



Diffuse large B-cell lymphoma Lymph node shows a diffuse pattern of involvement, with loss of normal structures such as sinuses and lymphoid follicles. (From Warnke, RA, Weiss, LM, Chan, JK, Cleary, ML, Dorfman, RF. Tumors of the lymph nodes and spleen. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 14, 1995, Washington, DC. Armed Forces Institute of Pathology.)

Behavior

- Indolent – these lymphomas grow slowly. The majority of NHLs are considered indolent. Indolent lymphomas are generally considered incurable. (Follicular lymphoma)

- Aggressive – these lymphomas have a rapid growth pattern. This is the second most common form of NHL and are curable. (Diffuse large B- cell lymphoma)

- Very Aggressive – these lymphomas grow very rapidly. They account for a small proportion of NHLs and can be cured . Unless treated rapidly, these lymphomas can be life threatening. (Burkitt's lymphoma)

Low grade lymphomas carry the best prognosis(the most indolent and well tolerated malignancies) and high grade ones the worst(the highly proliferative and rapidly fatal).

International Prognostic Index

Five 'risk factors' should be identified in each pt. At the time of diagnosis

1) Age >60

2) LDH> normal

3) Performance status 2-4

4) Stage III or IV

5) Two or more extranodal sites such as GIT.

Score/risk category	5 yr survival
Score 0-1= low risk	73%
Score 2 = Low /Intermediate	51%
Score 3 = High/ Intermediate	43%
Score 4-5= High risk	26%

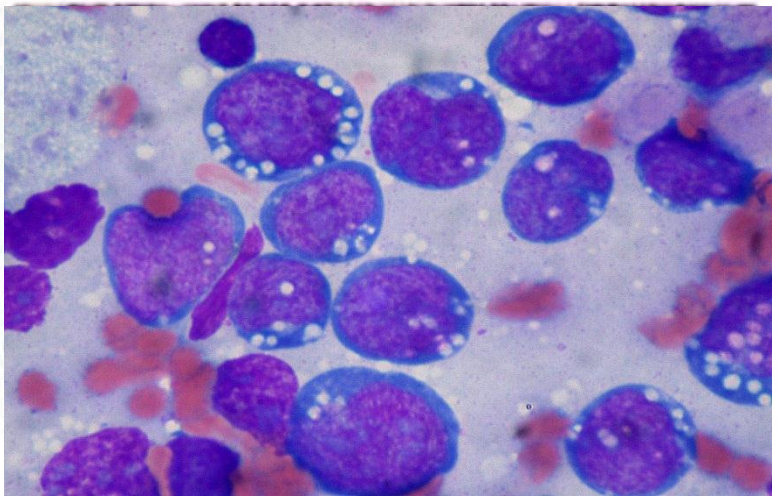
(Shipp et al Blood 1994:83:1165)

NHL: Ann Arbor Staging System

- Suffix ‘A’ means absence of B symptoms
- Suffix ‘B’ means presence of B symptoms
- Suffix ‘E’ means extra nodal disease
- Suffix ‘S’ means splenic involvement
- Suffix ‘X’ means bulky disease
- For example: Stage IIIB-S means disease above and below the diaphragm, with B symptoms and Splenic involvement

Burkitt's lymphoma: large B cell NHL

- Endemic in Africa
- Epstein Barr Virus (EBV)
- B Cell Lymphoma.
- Dark large B lymphocytes (malignant) with plenty of pale macrophages. (Starry sky pattern).



How to Diagnosis NHL

- The initial evaluation must establish:
  - The precise histologic type of NHL
  - The extent and sites of disease
  - The performance status of the patient
- All of this is important to establish prognosis and treatment

Where to start

- As always with the H&P:
- Key points to obtain in your “history”:
  - Lymphadenopathy: more than 2/3 of pt will present with peripheral adenopathy
    - Ask about waxing and waning of lymph nodes
    - As about the duration of lymphadenopathy

The History Cont'd

- B Symptoms:
  - Fever defined as T>38ºC
  - Weight loss defined by unexplained loss of >10% of body wt over 6 mos
  - Night sweats defined by **drenching** night sweats

The Physical Exam

- Exam all sites of potential involvement including:
  - Waldeyer's ring (tonsils, base of tongue, nasopharynx)
  - Std L.N. sites (cervical, inguinal, etc)
  - Liver and spleen
  - Abdominal L.N. (mesenteric, retroperitoneal)
  - Others: occipital, preauricular, epitrochlear, etc.

Unusual Sites/Presentations

- 10-35% will have primary extranodal NHL and about 50% will have extranodal disease during their illness
- Most common site of extranodal disease is the GI tract followed by the skin
- Symptoms from extranodal disease usually assoc with aggressive NHL

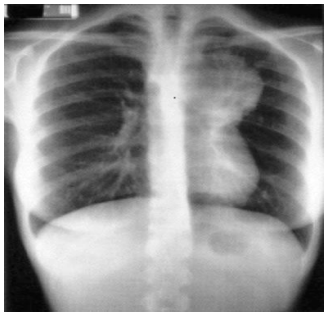
Extranodal Sites

- Renal involvement occurs in 2-14% of pts
- Rarer sites include: Testicular, prostate, bladder, ovary, orbit, heart, breast, salivary gland, thyroid and adrenal gland
- Examine skin carefully and biopsy any suspicious lesions

Diagnostic Lab tests

- Lymph node biopsy
- Bone marrow aspiration and biopsy - Staging
- CBC
- Immunohistochemistry
- Flow cytometry
- Cytogenetics
- LDH
- Uric acid
- HIV testing
- Immunoglobulin electrophoresis (paraprotein)

Staging study; Imaging tests



- CT chest/abd/pelvis
- PET scan